# High Pregnancy, Cord Blood, and Infant Vitamin D Concentrations May Predict Slower Infant Growth

Hauta-alus, Helena H.

2019-02

Hauta-alus , H H , Kajantie , E , Holmlund-Suila , E M , Rosendahl , J , Valkama , S M , Enlund-Cerullo , M , Helve , O M , Hytinantti , T K , Viljakainen , H , Andersson , S & Mäkitie , O 2019 , ' High Pregnancy, Cord Blood, and Infant Vitamin D Concentrations May Predict Slower Infant Growth ' , Journal of Clinical Endocrinology and Metabolism , vol. 104 , no. 2 , pp. 397-407 . https://doi.org/10.1210/jc.2018-00602

http://hdl.handle.net/10138/301119
https://doi.org/10.1210/jc.2018-00602

publishedVersion

# High Pregnancy, Cord Blood, and Infant Vitamin D Concentrations May Predict Slower Infant Growth

Helena H. Hauta-alus,[1] Eero Kajantie,[1,2,3,4] Elisa M. Holmlund-Suila,[1] Jenni Rosendahl,[1] Saara M. Valkama,[1] Maria Enlund-Cerullo,[1] Otto M. Helve,[1] Timo K. Hytinantti,[1] Heli Viljakainen,[5,6] Sture Andersson,[1] and Outi Mäkitie[1,7,8]

[1]Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki 00020, Finland; [2]National Institute for Health and Welfare, Helsinki 00271, Finland; [3]PEDEGO Research Unit, Me Oulu, Oulu University Hospital and University of Oulu, Oulu 90014, Finland; [4]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim 7491, Norway; [5]Folkhälsan Research Center, Helsinki 00014, Finland; [6]Department of Food and Environmental Sciences, University of Helsinki, Helsinki 00014, Finland; [7]Department of Molecular Medicine and Surgery, Karolinska Institutet, and Clinical Genetics, Karolinska University Laboratory, Karolinska University Hospital, Stockholm SE-17176, Sweden; and [8]Folkhälsan Institute of Genetics, Helsinki 00014, Finland

**ORCiD numbers:** 0000-0002-3487-7834 (H. H. Hauta-alus); 0000-0001-7081-8391 (E. Kajantie); 0000-0002-7486-3437 (H. Viljakainen); 0000-0002-4547-001X (O. Mäkitie).

**Context:** The relationship of maternal and infant 25-hydroxyvitamin D concentration [25(OH)D] with infant growth is unclear.

**Objective:** Our objective was to explore whether 25(OH)D in pregnancy, umbilical cord blood (UCB), or in infancy was associated with infant growth.

**Design:** This study involved 798 healthy infants and their mothers in Finland. We assessed 25(OH)D during pregnancy, from UCB at birth, and from the infant at the age of 12 months.

**Main Outcome Measures:** Infant length, weight, length-adjusted weight, and head circumference at 6 and 12 months and midupper-arm circumference at 12 months.

**Results:** Of the mothers and infants, 96% and 99% were vitamin D sufficient [25(OH)D ≥50 nmol/L], respectively. Mothers with pregnancy 25(OH)D >125 nmol/L had the shortest, lightest (in weight), and thinnest (in length-adjusted weight) infants at 6 months ($P$ for all $< 0.05$). For each 10 nmol/L higher UCB 25(OH)D, the infants were 0.03 SD score (SDS) shorter at 6 months (95% CI −0.05 to −0.01), adjusted for birth size, infant 25(OH)D, and parental height. Higher UCB 25(OH)D associated with smaller head circumference at 6 and 12 months ($P$ for all <0.05) but attenuated after adjustments. Mothers with pregnancy 25(OH)D >125 nmol/L had the thinnest infants at 12 months ($P = 0.021$). For each 10 nmol/L higher infant 25(OH)D, the infants were 0.03 SDS lighter (−0.05 to −0.01) and 0.03 SDS thinner (−0.05 to 0.00) at 12 months.

**Conclusions:** Our results suggest that high pregnancy, cord blood, and infant vitamin D concentration may have disadvantageous effects on infant growth. (***J Clin Endocrinol Metab*** **104: 397–407, 2019)**

Several studies have associated poor maternal vitamin D status with fetal growth restriction (1–3). The few studies examining whether and how maternal or infant vitamin D status affect postnatal growth in the infant show inconsistent results. Many observational studies have found no association between maternal vitamin D status and linear growth in infants or older children (4–8). However, a randomized trial of maternal vitamin

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 15 March 2018. Accepted 17 September 2018.
First Published Online 20 September 2018

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; MUAC, midupper-arm circumference; SDS, SD score; UCB, umbilical cord blood; VIDI, Vitamin D Intervention in Infants.

D supplementation in Bangladesh, with mean baseline 25-hydroxyvitamin D [25(OH)D] concentration of 42 nmol/L, resulted in greater offspring length at 12 months of age (9).

In children, severe vitamin D deficiency increases the risk of rickets, which can lead to growth impairment (10). Indeed, among low-birth-weight infants in India, among whom vitamin D deficiency was common, a weekly vitamin D supplementation of 35 μg improved infant linear growth compared with placebo (11). However, a Canadian vitamin D intervention study (with vitamin D doses of 10, 20, 30, and 40 μg) in 132 healthy infants showed no difference between the groups in growth at 11 months despite different 25(OH)D, although this study may have been underpowered (12).

Previous studies have largely lacked subjects with high 25(OH)D concentrations and have focused on the effects of very low vitamin D status or vitamin D supplementation in vitamin D–deficient children on infant growth. In addition, studies have rarely included data for both maternal and infant 25(OH)D concentrations. In Finland, vitamin D supplementation is recommended for pregnant women and all children, and vitamin D food fortification is used in liquid dairy products and fat spreads (13). Our objective was to explore whether 25(OH)D in pregnancy, umbilical cord blood (UCB), or infancy at 12 months of age are associated with growth parameters in 6-month-old and 12-month-old infants. This study was part of the Vitamin D Intervention in Infants (VIDI) study, a randomized trial on vitamin D supplementation with the standard (10 μg) or a higher dose (30 μg) of vitamin $D_3$ in infants.

## Materials and Methods

### Subjects

At Kätilöopisto Maternity Hospital (Helsinki, Finland), 987 families were recruited into the VIDI study between January 2013 and June 2014, during the mother's hospital stay after delivery. Written informed consent was obtained from the parents at recruitment. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. Ethical approval was obtained from the Research Ethics Committee of the Hospital District of Helsinki and Uusimaa (107/13/03/03/2012). The project protocol is registered at clinicaltrials.gov (NCT01723852). According to the inclusion criteria, the mothers were of Northern European origin without regular medication and with singleton pregnancy. Exclusion criteria for the newborns were: nasal continuous positive airway pressure treatment or need for nasogastric tube >1 day, intravenous glucose infusion, seizures, and duration of phototherapy >3 days. The infants were born between 37 and 42 weeks of gestation with birth weights appropriate for gestational age [SD score (SDS) between −2.0 and 2.0].

Infants were randomized to receive daily vitamin $D_3$ supplementation with either 10 μg or 30 μg from age 2 weeks to 24 months. We have previously reported that at the age of 12 months, in addition to the supplemental dose, nonbreastfed infants (n = 476) received 0.6 to 28.3 and breastfed infants (n = 263) 0 to 30.7 μg of vitamin D daily from food (14). The VIDI study included three study visits at the ages of 6, 12, and 24 months and multiple retrospectively and prospectively collected questionnaires. A detailed description of the recruitment and study protocol has been reported previously (15).

Of the recruited 987 families, 12 did not meet the inclusion criteria and were excluded, leaving 975 study participants. In addition, 87 infants withdrew prior to 6 months, and a further 15 withdrew prior to 12 months, leaving 873 infants with body size measurements. Of these infants, 74 did not have 25(OH)D measurements, and 1 infant was excluded after a diagnosis of Rieger syndrome. The final study cohort for this study thus comprised 798 infants (Supplemental Figure 1). Of the infants, 51% (409 out of 798) were girls. Number of subjects varies in different analyses due to partial missing data and is reported in the tables. As data on the infants' vitamin D supplemental dose were unavailable for this study, we adjusted the analyses for Infant 25(OH)D at 12 months as a marker of total vitamin D intake including supplements.

### Biochemical analyses

25(OH)D measurements were obtained at three time points for each subject. Pregnancy serum samples were collected at prenatal clinics on average (SD) at gestational week 11 (2) between June 2012 and February 2014 as part of the mothers' normal follow-up [hereafter referred to as Pregnancy 25(OH)D]. Pregnancy samples were stored in the Finnish Maternity Cohort serum bank organized by the National Institute for Health and Welfare. UCB for 25(OH)D measurement was obtained at birth (gestational weeks 37 to 42) between January 2013 and June 2014 [hereafter referred to as UCB 25(OH)D]. At the 12-month follow-up visit, infant serum samples were obtained between December 2013 and June 2015 and analyzed for 25(OH)D [hereafter referred to as Infant 25(OH)D] and intact PTH.

Pregnancy serum and UCB plasma 25(OH)D were analyzed simultaneously, and Infant serum 25(OH)D and PTH in a separate series using the IDS-iSYS fully automated immunoassay system with chemiluminescence detection (Immunodiagnostic Systems Ltd., Bolton, United Kingdom) with intra-assay variation <7% for Pregnancy 25(OH)D, Infant 25(OH)D, and PTH and <13% for UCB 25(OH)D. Detailed information on UCB plasma 25(OH)D (16) and Pregnancy 25(OH)D analysis (17) has been previously reported. The quality and accuracy of the 25(OH)D analyses are validated on an ongoing basis by participation in the vitamin D External Quality Assessment Scheme (Charing Cross Hospital, London, United Kingdom). The method showed a ≤8% positive bias against National Institute of Standards and Technology Reference Measurement Procedure.

We defined vitamin D deficiency as 25(OH)D <50 nmol/L (18) and vitamin D sufficiency as 25(OH)D ≥50 nmol/L (19). Furthermore, we divided subjects into groups based on 25(OH)D concentrations using an additional cutoff values of 75 nmol/L, which has been considered a lower threshold value for bone health (18), and 125 nmol/L, above which values have been related to health risks (19).

### Parental data

Parental data were obtained from a self-administered baseline questionnaire, filled out after delivery, and from medical records. Parental heights (centimeters) and weights (kilograms) before

pregnancy and parity were collected primarily from the prenatal maternity card or from our baseline questionnaire. Parental heights were standardized into sex-specific $z$ scores. Prepregnancy body mass index (BMI) was calculated (kilograms per meters squared). Duration of gestation was determined by first-trimester ultrasound examination.

Parental education level was categorized into lower and higher education (lower is lower or upper secondary or postsecondary nontertiary education or less than a bachelor degree, and higher is first or second stage of tertiary education or at least a bachelor degree), according to the highest received degree of the parents. Parental smoking status was assessed before pregnancy and at infant age of 24 months and applied as a merged previous and current smoking status. Family income level was inquired with a questionnaire completed at infant age of 24 months.

### Infant data

Birth size was measured by midwives according to standard procedure, and we collected data from birth records. Infant weight (kilograms), length (centimeters), and head circumference (centimeters) were measured at the 6-month and 12-month follow-up visits by a pediatrician or a research nurse. In addition, at the 12-month follow-up visit, midupper-arm circumference (MUAC; millimeters) was measured. Length was measured with a tabletop meter in a supine position and weight with an electronic scale (Seca GmbH, Hamburg, Germany). Weight, length, length-adjusted weight, and head circumference were expressed as SDS using age-specific and sex-specific Finnish references (20). Weight, length, length-adjusted weight, and head circumference were considered normal when between −2.0 and 2.0 SDS. MUAC was standardized into sex-specific $z$ score within the current study population, as no Finnish normative data exist. Duration of breastfeeding was determined based on repeated questionnaires in prospectively collected study diaries.

### Statistical analysis

The normality of the variables was visually inspected. Infant and family characteristics were reported as means, SDs, and percentages. Nonparametric methods were used where appropriate. Independent variables were Pregnancy, UCB, and Infant 25(OH)D concentrations, and outcome variables were infant size at 6 and 12 months of age (9 outcomes altogether). Covariates were chosen based on their statistically significant association with several outcome measures. To assess the independent effect of Pregnancy and UCB 25(OH)D on growth, we adjusted the analyses for Infant 25(OH)D concentration at 12 months of age as a marker of the postnatal supplemental vitamin D intake. Missing values of covariates were multiple imputed (five imputations). In tables with infant and family characteristics (Tables 1 and 2), all values are nonimputed.

A change in infant growth (length, weight, length-adjusted weight, and head circumference) between birth and 6 and 12 months of age was calculated by saving the residuals from linear regression models of body size SDS at each successive age vs the corresponding body size SDS at all earlier ages (21). These residuals were referred to as "conditional growth." The corresponding birth size and size at 6 months of age were adjusted for in the analyses of conditional growth. Using conditional growth indicators as outcomes enabled us to explore whether 25(OH)D had an effect on the growth rate among different growth periods.

Univariate and multivariate linear regression analysis was used to explore associations between 25(OH)D and infant growth and conditional growth. We used three regression models. In the tables, we show an unadjusted model 1 and model 2, which is adjusted for variables that are essential to describe the association between 25(OH)D concentration and early growth independent of genetic determinants of growth. These variables included SDS of the corresponding birth size, maternal and paternal height $z$ scores, and Infant 25(OH)D [except in analyses in which Infant 25(OH)D served as the independent variable]. In the text, we report model 3, which is further adjusted for potential confounders that can be expected to have a causal effect on the predictor and outcome: maternal and paternal prepregnancy BMI, parental smoking status, parental education level, family income level, and duration of breastfeeding. The analyses on conditional growth were conducted in a similar manner. Quadratic associations were explored with linear regression by adding the corresponding 25(OH)D squared in the growth models 1 and 2. In models of linear regression, residuals were plotted to assess their normal distribution and evaluate heteroscedasticity.

Infant size was investigated in categories of 25(OH)D with analysis of covariance adjusted for corresponding birth size SDS, maternal and paternal height $z$ scores, and Infant 25(OH)D [except in analyses in which Infant 25(OH)D served as the independent variable]. Differences in infant size were compared between categories of 25(OH)D with linear regression using the 25(OH)D category of 50 to 74.9 nmol/L as a reference group. Statistical significance was determined at $P < 0.05$. All statistical analyses were conducted using the IBM SPSS program for Windows, version 22 (IBM, Chicago, IL).

## Results

Infant and family characteristics are presented in Tables 1 and 2. Almost all infants had normal body size (weight and length between −2.0 and 2.0 SDS) at 6 and 12 months of age. Of the infants, 79% were partially breastfed at 6 months and 40% at 12 months of age. Of the mothers, 96% were vitamin D sufficient [25(OH)D ≥50 nmol/L], and 99% of the infants were vitamin D sufficient. Altogether, 2% of Pregnancy, 4% of UCB, and 17% of Infant 25(OH)D values were >125 nmol/L, ranging up to 189 nmol/L, 284 nmol/L, and 241 nmol/L, respectively. Correlation coefficient between Pregnancy and UCB 25(OH)D was $r = 0.27$ ($P < 0.001$); between UCB and Infant at 12 months, 25(OH)D was $r = 0.15$ ($P < 0.001$); and between Pregnancy and Infant at 12 months, 25(OH)D was $r = 0.07$ ($P = 0.081$). Infants' PTH concentration at 12 months declined with increasing Infant 25(OH)D concentration (Supplemental Table 1).

All linear and quadratic associations between 25(OH)D concentrations and infant growth are shown in Tables 3 and 4. Conditional growth results are shown in Supplemental Tables 2 and 3. We categorized 25(OH)D concentrations into four groups: <50 nmol/L, 50 to 74.9 nmol/L

**Table 1. Infant Characteristics (n = 798)**

| | At Birth | At 6 Mo | At 12 Mo |
|---|---|---|---|
| Gestational age, wk | 40.2 (1.1) | — | — |
| Age, mo | — | 6.0 (0.2) | 12.0 (0.4) |
| Length, cm | 50.4 (1.7) | 67.5 (2.2) | 75.3 (2.5) |
| Length, SDS | −0.19 (0.88) | −0.47 (0.97) | −0.54 (1.01) |
| Weight, kg | 3.5 (0.4) | 8.0 (0.9) | 9.8 (1.1) |
| Weight, SDS | −0.26 (0.79) | 0.21 (1.07) | −0.24 (1.01) |
| Length-adjusted weight, SDS | 0.07 (0.94) | 0.15 (1.11) | 0.02 (1.02) |
| Head circumference, cm[a] | 35.2 (1.4) | 43.6 (1.2) | 46.5 (1.2) |
| Head circumference, SDS[a] | −0.16 (0.97) | −0.30 (0.94) | −0.42 (0.94) |
| MUAC, cm[b] | — | — | 15.3 (1.2) |
| Blood 25(OH)D, nmol/L [range][c] | 82.5 (25.8) [36.7–283.7] | — | 98.9 (29.0) [23.0–241.0] |
| Blood 25(OH)D ≥50 nmol/L, %[c] | 96 | — | 99 |
| Normal length SDS (−2.0 to 2.0), % | 98 | 94 | 93 |
| Normal weight SDS (−2.0 to 2.0), % | 100 | 94 | 96 |
| Normal length-adjusted weight SDS (−2.0 to 2.0), % | 96 | 94 | 96 |
| Normal head circumference SDS (−2.0 to 2.0), %[a] | 95 | 96 | 96 |
| Breastfed, %[d] | — | 79 | 40 |
| Sex, female, % | 51 | 51 | 51 |

Data are means (SD) unless stated otherwise. Dash indicates no data available.

[a]At birth, 2 values are missing; at 6 mo follow-up, 21 values are missing; and at 12 mo follow-up, 5 values are missing.

[b]Total of 39 values are missing.

[c]Samples at birth are from UCB, and 18 values are missing. Samples at 12 mo are from infant serum.

[d]Total of 13 values are missing.

(reference group), 75 to 125 nmol/L, and >125 nmol/L (Figs. 1 and 2). Infant growth in the lowest and the two highest 25(OH)D groups was compared with the reference group of 50 to 74.9 nmol/L. Pregnancy 25(OH)D predicted length-adjusted weight at 6 and 12 months (Tables 3 and 4). At 6 months, mothers whose Pregnancy 25(OH)D was >125 nmol/L had the shortest (in length; mean difference 0.41 SDS; $P = 0.048$), lightest (in weight; mean difference 0.63 SDS; $P = 0.016$), and thinnest (in length-adjusted weight; mean difference 0.70 SDS; $P = 0.013$) infants compared with the reference group (Fig. 1). We found a quadratic association between Pregnancy 25(OH)D and length at 12 months (Table 4). We also observed an inverse association between Pregnancy 25(OH)D and MUAC (Table 4). The 12-month MUAC was smaller in the group with Pregnancy 25(OH)D at 75 to 125 nmol/L (mean difference 0.17 SDS; $P = 0.049$) compared with the reference group (Fig. 2). At 12 months of age, infants of mothers with the highest Pregnancy 25(OH)D were the thinnest (mean difference 0.60 SDS; $P = 0.021$) compared with the reference group (Fig. 2).

Infants with higher UCB 25(OH)D were shorter at 6 months (Table 3) and had a smaller head circumference at 6 and 12 months, although this attenuated to non-significance when adjusted (Tables 3 and 4). Furthermore, infants with UCB 25(OH)D >125 nmol/L were the shortest at 6 months compared with the reference group (mean difference 0.39 SDS; $P = 0.011$) (Fig. 1). As demonstrated by conditional lengths, infants with higher UCB 25(OH)D grew more slowly between birth and 6 months but more rapidly between 6 and 12 months (Supplemental Tables 2 and 3). Newborns with UCB 25(OH)D <50 nmol/L were the thinnest at 6 months (mean difference 0.45 SDS; $P = 0.034$) compared with the reference group (Fig. 1).

**Table 2. Family Characteristics**

| | n | Mean (SD) |
|---|---|---|
| Maternal age, y | 798 | 31.7 (4.3) |
| Paternal age, y | 759 | 33.6 (5.3) |
| Maternal height, cm | 798 | 166.4 (6.0) |
| Paternal height, cm | 778 | 180.3 (6.6) |
| Maternal prepregnancy BMI | 794 | 23.2 (3.6) |
| Paternal prepregnancy BMI | 771 | 25.7 (3.4) |
| Pregnancy 25(OH)D, nmol/L [range] | 671 | 82.4 (20.3) [24.8–189.2] |
| Pregnancy sampling, gestational wk | 671 | 11.3 (2.2) |
| Pregnancy 25(OH)D ≥50 nmol/L, % | 671 | 96 |
| Parity, primipara, % | 797 | 63 |
| Maternal smoking, yes, %[a] | 793 | 16 |
| Paternal smoking[1], yes, % | 784 | 26 |
| Parental education, higher, %[b] | 789 | 81 |
| Family income level | 689 | |
| <40,000 €/y, % | | 19 |
| 40,000–89,000 €/y, % | | 60 |
| >90,000 €/y, % | | 21 |

Data are means (SD) unless stated otherwise.

[a]Previous and current smoking status.

[b]Higher education reflects at least a bachelor level education.

**Table 3. Associations Between 25(OH)D Concentrations and Infant Growth at 6 mo Follow-up**

| | SDS at 6 mo Follow-up | | | |
|---|---|---|---|---|
| | Length | Weight | Length-Adjusted Weight | Head Circumference[a] |
| Pregnancy 25(OH)D, 10 nmol/L, n = 671 | | | | |
| Model 1, unadjusted | −0.02 (−0.06 to 0.01) | −0.03 (−0.07 to 0.01) | −0.03 (−0.07 to 0.01) | −0.02 (−0.05 to 0.02) |
| *P* value for linear association | 0.22 | 0.15 | 0.17 | 0.36 |
| *P* value for quadratic association | 0.92 | 0.15 | 0.02 | 0.08 |
| Model 2, adjusted[b] | −0.02 (−0.05 to 0.01) | −0.03 (−0.07 to 0.00) | −0.03 (−0.07 to 0.01) | −0.02 (−0.05 to 0.01) |
| *P* value for linear association | 0.12 | 0.08 | 0.13 | 0.22 |
| *P* value for quadratic association | 0.45 | 0.32 | 0.02 | 0.12 |
| UCB 25(OH)D, 10 nmol/L, n = 780 | | | | |
| Model 1, unadjusted | −0.04 (−0.06 to −0.01) | −0.01 (−0.04 to 0.02) | 0.00 (−0.03 to 0.03) | −0.03 (−0.06 to −0.01) |
| *P* value for linear association | 0.006 | 0.55 | 0.84 | 0.01 |
| *P* value for quadratic association | 0.49 | 0.42 | 0.83 | 0.79 |
| Model 2, adjusted[b] | −0.03 (−0.05 to −0.01) | 0.00 (−0.01 to 0.02) | 0.01 (−0.02 to 0.04) | −0.02 (−0.03 to 0.00) |
| *P* value for linear association | 0.008 | 0.87 | 0.51 | 0.20 |
| *P* value for quadratic association | 0.28 | 0.19 | 0.57 | 0.52 |

Data are $\beta$ coefficients (95% CI) per 10 nmol/L higher in 25(OH)D concentration based on linear regression.

[a]Number of subjects vary in analyses due to missing values of head circumferences; for Pregnancy 25(OH)D in model 1, n = 650 and in model 2, n = 649; for UCB 25(OH)D in model 1, n = 759 and in model 2, n = 757.

[b]Model 2 is adjusted for the corresponding birth size SDS, maternal and paternal height *z* scores, and Infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake [except for Infant 25(OH)D].

A higher Infant 25(OH)D at 12 months was associated with smaller length, weight, length-adjusted weight, and head circumference at 12 months, although the associations with length and head circumference attenuated with adjustments (Table 4). Furthermore, infants with 25(OH)D >125 nmol/L at 12 months had the smallest weight (mean difference 0.25 SDS; $P = 0.022$) and length-adjusted weight (mean difference 0.25 SDS; $P = 0.032$) compared with the reference group (Fig. 2).

For the regression analyses assessing the relationship between 25(OH)D concentrations and growth (Tables 3 and 4), we further adjusted for the following potential confounding factors: maternal and paternal prepregnancy BMI, parental smoking status, parental education level, family income level, and duration of breastfeeding) (data not shown). Results remained similar except for the association between Pregnancy 25(OH)D and MUAC at 12 months of age, which disappeared.

## Discussion

In this study, we demonstrate that high 25(OH)D in the mother and infant were associated with slower postnatal growth in a large prospective study of healthy full-term infants. This study is among the few to explore whether maternal and infant vitamin D statuses were associated with growth parameters in 6- and 12-month-old infants. The study was carried out in a population of northern latitude but where severe vitamin D deficiency is rare. Almost all mothers and infants were vitamin D sufficient [25(OH)D ≥50 nmol/L]. Our main finding was counterintuitive: high 25(OH)D in pregnancy, UCB, and infancy associated with delayed growth in infants.

The main findings showed that mothers with Pregnancy 25(OH)D >125 nmol/L had the shortest (in length), lightest (in weight), and thinnest (in length-adjusted weight) infants at 6 months of age. Infants of these mothers also had the lowest length-adjusted weight at 12 months of age. Similarly, infants with higher UCB 25(OH)D were shorter at 6 months of age, but those with 25(OH)D <50 nmol/L were the lightest. As for length, we observed a slow linear growth until the age of 6 months and an accelerated growth from 6 to 12 months of age in those with higher UCB 25(OH)D. Furthermore, infants with higher vitamin D status at 12 months had lower weight and length-adjusted weight at 12 months

**Table 4. Associations Between 25(OH)D Concentrations and Infant Growth at 12 mo Follow-up**

| | SDS | | | | *z* Score |
|---|---|---|---|---|---|
| | Length | Weight | Length-Adjusted Weight | Head Circumference[a] | MUAC[b] |
| Pregnancy 25(OH)D, 10 nmol/L, n = 671 | | | | | |
| Model 1, unadjusted | −0.01 (−0.05 to 0.03) | −0.02 (−0.06 to 0.01) | −0.03 (−0.07 to 0.01) | −0.02 (−0.05 to 0.02) | −0.04 (−0.08 to 0.00) |
| *P* value for linear association | 0.62 | 0.20 | 0.16 | 0.39 | 0.04 |
| *P* value for quadratic association | 0.11 | 0.29 | 0.02 | 0.48 | 0.37 |
| Model 2, adjusted[c] | −0.01 (−0.05 to 0.02) | −0.03 (−0.06 to 0.01) | −0.03 (−0.07 to 0.01) | −0.02 (−0.05 to 0.02) | −0.04 (−0.08 to 0.00) |
| *P* value for linear association | 0.44 | 0.13 | 0.15 | 0.30 | 0.04 |
| *P* value for quadratic association | 0.02 | 0.52 | 0.01 | 0.65 | 0.37 |
| UCB 25(OH)D, 10 nmol/L, n = 780 | | | | | |
| Model 1, unadjusted | −0.01 (−0.03 to 0.02) | −0.01 (−0.04 to 0.01) | −0.02 (−0.04 to 0.01) | −0.03 (−0.05 to 0.00) | −0.02 (−0.04 to 0.01) |
| *P* value for linear association | 0.59 | 0.28 | 0.27 | 0.045 | 0.26 |
| *P* value for quadratic association | 0.97 | 0.91 | 0.82 | 0.49 | 0.79 |
| Model 2, adjusted[c] | 0.00 (−0.03 to 0.02) | 0.00 (−0.02 to 0.01) | −0.01 (−0.04 to 0.02) | −0.01 (−0.02 to 0.00) | −0.01 (−0.04 to 0.01) |
| *P* value for linear association | 0.87 | 0.76 | 0.54 | 0.44 | 0.38 |
| *P* value for quadratic association | 0.89 | 0.74 | 0.88 | 0.27 | 0.58 |
| Infant 25(OH)D, 10 nmol/L, n = 798 | | | | | |
| Model 1, unadjusted | −0.03 (−0.05 to 0.00) | −0.03 (−0.06 to −0.01) | −0.02 (−0.05 to 0.00) | −0.02 (−0.05 to 0.00) | −0.02 (−0.04 to 0.01) |
| *P* value for linear association | 0.04 | 0.009 | 0.049 | 0.03 | 0.15 |
| *P* value for quadratic association | 0.33 | 0.04 | 0.06 | 0.42 | 0.35 |
| Model 2, adjusted[c] | −0.02 (−0.04 to 0.00) | −0.03 (−0.05 to −0.01) | −0.03 (−0.05 to 0.00) | −0.02 (−0.04 to 0.01) | −0.02 (−0.04 to 0.01) |
| *P* value for linear association | 0.11 | 0.01 | 0.02 | 0.16 | 0.12 |
| *P* value for quadratic association | 0.58 | 0.06 | 0.04 | 0.61 | 0.35 |

Data are $\beta$ coefficients (95% CI) per 10 nmol/L higher in 25(OH)D concentration based on linear regression.

[a]Number of subjects vary in analyses due to missing values of head circumferences; for Pregnancy 25(OH)D in model 1, n = 666 and in model 2, n = 665; for UCB 25(OH)D in model 1, n = 775 and in model 2, n = 773; for Infant 25(OH)D in model 1, n = 793 and in model 2, n = 791.

[b]Number of subjects vary in analyses due to missing values of MUAC; for Pregnancy 25(OH)D, n = 644; for UCB 25(OH)D, n = 742; and for Infant 25(OH)D, n = 760.

[c]Model 2 is adjusted for the corresponding birth size SDS (except for MUAC; the covariate was length-adjusted birth weight), maternal and paternal height *z* scores, and Infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake [except when Infant 25(OH)D was dependent].

of age, with the lightest and thinnest infants having 25(OH)D >125 nmol/L. These results give insight into how vitamin D status affects postnatal growth in healthy infants in a mostly vitamin D–sufficient population.

Evidence has been inconsistent concerning associations between maternal vitamin D status and postnatal growth. The few studies in populations with relatively low 25(OH)D have found positive (22, 23), negative (23), or lacking (24) associations between maternal 25(OH)D and infant length or weight among 1- to 6-month-old infants. In Gambian mothers with relatively high mean pregnancy 25(OH)D (103 to 111 nmol/L), vitamin D status was unrelated to infant growth at 3 months of age (25). However, we found that higher Pregnancy and UCB 25(OH)D predicted slower infant growth until 6 months of age. In the Bangladeshi study with 134 infants, of which 26% were stunted during the follow-up, maternal supplementation of 875 μg/wk resulted in divergent mean UCB 25(OH)D between supplemented and placebo-treated mothers (103 vs 39 nmol/L) (9). Opposed to our findings, this study found that maternal supplementation increased infant length at 1 and 2 months but no longer at 4 and 6 months and then again at 12 months of age (9). In older infants (9 to

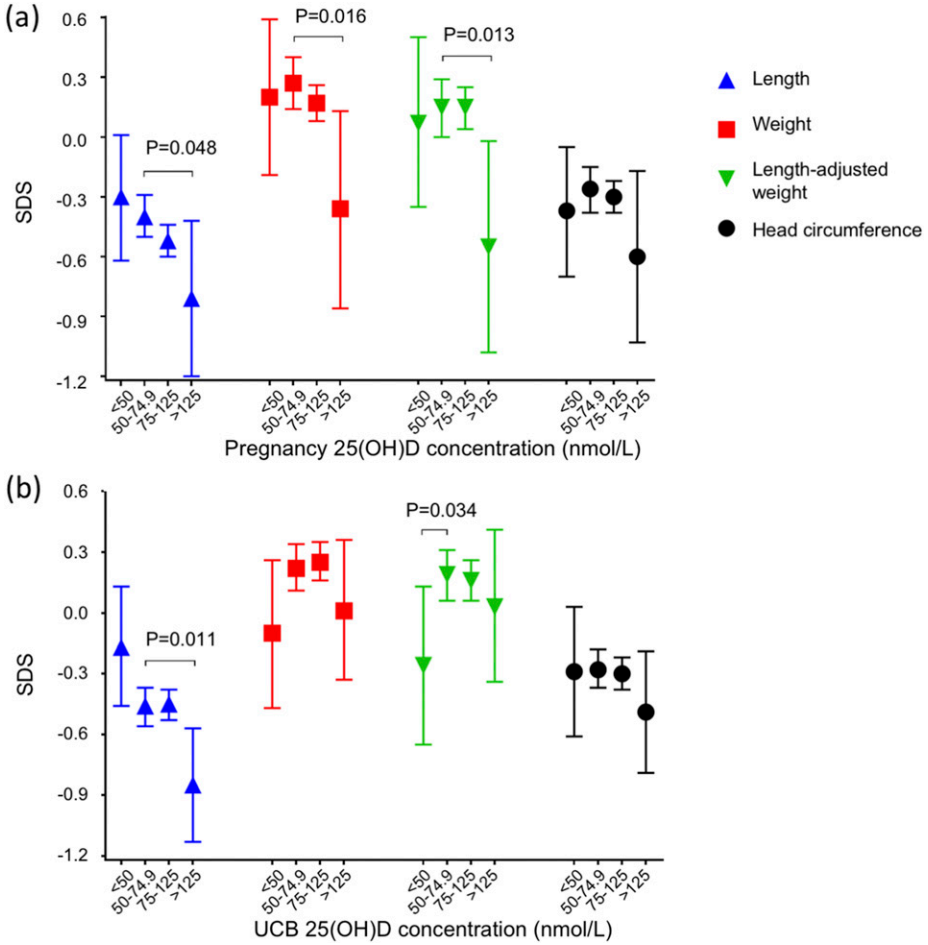


**Figure 1.** The effect of (a) Pregnancy (n = 671) and (b) UCB (n = 780) 25(OH)D on infant growth parameters at the age of 6 months. 25(OH)D concentration is expressed in categories of <50 nmol/L, 50–74.9 nmol/L (reference group), 75–125 nmol/L, and >125 nmol/L. Values are means with 95% CIs adjusted for corresponding birth size SDS, maternal and paternal height *z* scores, and Infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake. *P* values are only shown if statistically significant ($P < 0.05$) between the reference group and other groups. Number of subjects in Pregnancy 25(OH)D categories: <50, n = 25; 50–74.9, n = 218; 75–125, n = 412; and >125, n = 16; and in UCB 25(OH)D: <50, n = 29; 50–74.9, n = 294; 75–125, n = 425; and >125, n = 32.

18 months), the relation of maternal vitamin D status with infant growth has similarly been conflicting (5, 6, 8, 9, 22, 23, 25). In our study, the possibly disadvantageous effect of high Pregnancy and UCB 25(OH)D on several infant growth indicators remained to some extent until 12 months of age. Our finding is somewhat contrary to a Dutch multiethnic study, in which slow fetal growth but enhanced postnatal growth was observed in infants of mothers with 25(OH)D <30 nmol/L compared with those with 25(OH)D >50 nmol/L (23). However, our results may suggest a similar catch-up growth but, in contrast, in infants of mothers with high 25(OH)D. Together, these results may indicate an inverse U-shaped association between maternal 25(OH)D and infant growth, as has been proposed to exist between maternal vitamin D status and fetal growth (26, 27). We previously reported in this cohort an inverse relationship between UCB 25(OH)D and newborn head circumference (17). This finding was still apparent at 6 and 12 months but attenuated when adjusting for birth head circumference and parental height.

In addition to Pregnancy and UCB 25(OH)D, also high Infant 25(OH)D was negatively associated with postnatal growth; the strongest associations appeared with weight and length-adjusted weight. These findings are in line with a Danish study that found 25(OH)D (mean 77 nmol/L) at 9 months to associate negatively with length and BMI (28). However, two previous vitamin D supplementation trials in infants found no effect on growth between different dosages (12, 29). By contrast, in Indian low-birth-weight infants, the vitamin D supplementation from the age of 1 week until 6 months increased infant length and weight at 6 months but no longer at 3 to 6 years (11). In that study, vitamin D deficiency was highly prevalent in the placebo group (73%) (11). The inconsistent findings on vitamin D and infant postnatal growth may be due to ethnic, genetic, geographical, nutritional status, and lifestyle differences

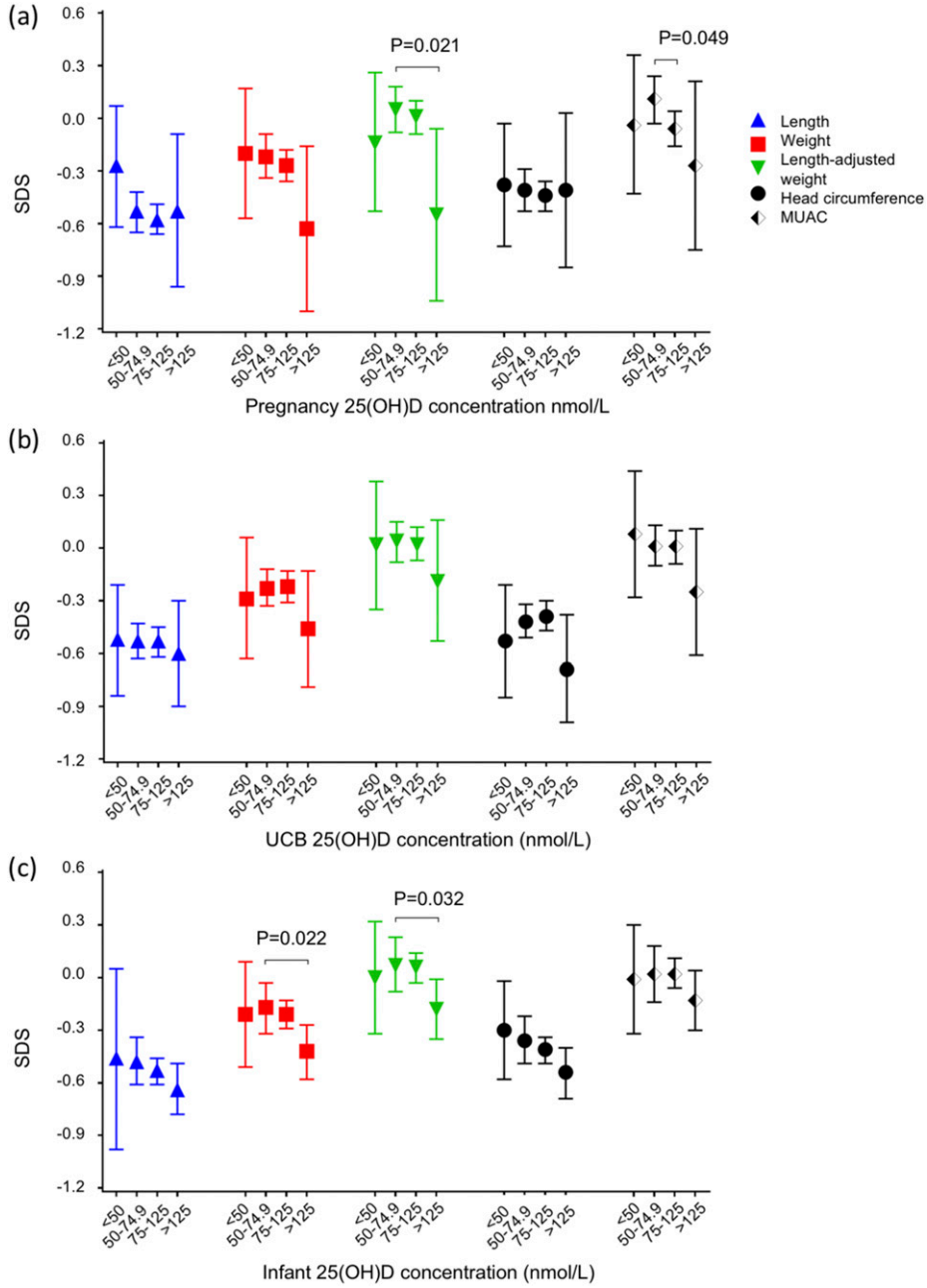


**Figure 2.** The effect of (a) Pregnancy (n = 671), (b) UCB (n = 780), and (c) Infant (n = 798) 25(OH)D on infant growth parameters at the age of 12 months. 25(OH)D concentration is expressed in categories of <50 nmol/L, 50–74.9 nmol/L (reference group), 75–125 nmol/L, and >125 nmol/L. Values are means with 95% CIs adjusted for corresponding birth size SDS (except for MUAC; the covariate was length-adjusted birth weight), maternal and paternal height *z* scores, and Infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake [except when Infant 25(OH)D was independent]. *P* values are only shown if statistically significant ($P < 0.05$) between the reference group and other groups. Number of subjects in Pregnancy 25(OH)D categories: <50, n = 25; 50–74.9, n = 218; 75–125, n = 412; and >125, n = 16, in UCB 25(OH)D: <50, n = 29; 50–74.9, n = 294; 75–125, n = 425; and >125, n = 32; and in Infant 25(OH)D: <50, n = 10; 50–74.9, n = 160; 75–125, n = 493; and >125, n = 135.

among study populations (30–32) and, above all, differences in 25(OH)D concentrations. However, this is difficult to prove, as there is a lack of study populations with both low and high 25(OH)D values. Furthermore, previous studies have applied varying cutoff values for 25(OH)D (8, 31). Ong *et al.* (8) suggested that severe vitamin D deficiency (<30 nmol/L) may impair child growth, but beyond that, there might not be any association between vitamin D status and early life growth. However, studies involving populations with especially high 25(OH)D are limited, and many studies have presented only restricted group-level data.

Taken together, our results suggest that an inverse U-shaped association may exist between 25(OH)D and postnatal growth, as slower growth was more evident in the group of 25(OH)D <50 nmol/L and >125 nmol/L in

several growth parameters, although the limited number of subjects in both extreme ends of the 25(OH)D range constrained our analysis. The inverse U-shaped or J-shaped relationship between vitamin D status and health is supported by observations in adults (33). In addition, our previous finding of a positive association between UCB 25(OH)D and inflammatory markers further support the possible adverse effect of high 25(OH)D on infant health (34). The rather high Pregnancy and UCB 25(OH)D in our cohort can be explained by the fact that almost all mothers (95%) in our study were taking vitamin D supplements during pregnancy, with a mean daily intake of 16 μg (16). In addition, vitamin D–fortified foods are commonly used in Finland (13). In addition to vitamin D, folic acid is also recommended for pregnant women in Finland, from the planning of pregnancy until gestational week 12; however, this recommendation was not valid at the time of this study. Iron supplementation is not routinely recommended. With regard to infants, based on the VIDI study protocol, infants received vitamin D supplements of 10 μg or 30 μg daily, leading to relatively high 25(OH)D. Because our study only included infants born term with normal birth weight, it remains unknown whether these results can be extrapolated to children born preterm or with low or high birth weight.

Infant growth is regulated by several factors, including those related to mineral homeostasis, circulating endocrine factors, and local regulators of the growth plate function. The nature of our study did not allow us to explore potential mechanisms for adverse growth outcomes caused by high 25(OH)D concentrations. High vitamin D status may affect calcium and phosphate homeostasis. However, we have previously shown that whereas Infant 25(OH)D correlated positively with ionized calcium concentration, no severe hypercalcemia developed (35). Furthermore, our previous study showed that urine calcium excretion was similar in 3-month-old infants supplemented with 10, 30, or 40 μg vitamin $D_3$ and that 25(OH)D did not correlate with bone parameters (29). In the current study, the mean PTH concentration was lower in the higher 25(OH)D category, suggesting that there may be mild changes that could impact growth plate function (36) via the PTH-PTH–related peptide axis or the calcium-sensing receptor (37). We did not measure $1,25(OH)_2$ vitamin D [$1,25(OH)_2D$] concentrations, but it is possible that high 25(OH)D leads to increased $1,25(OH)_2D$, which in turn may have a negative effect on growth due to increased osteoclastogenesis (38). In genetically modified mice, high maternal $1,25(OH)_2D$ levels adversely affected the total amount of calcium stored in fetal bones (39). The GH–IGF-1 axis plays an important role in the regulation of childhood growth, and although some studies have shown a positive effect of vitamin D supplementation on IGF-1 in children (40), it is unknown whether supranormal 25(OH)D concentrations have a similar positive effect.

A strength and limitation of this study is in the recruitment, which took place in a single hospital; this enabled standardized data collection, but a multicenter study might have resulted in a more diverse study population. A limitation was the inability to use data on infant vitamin D supplementation because of the ongoing double-blind intervention. However, we applied the attained 25(OH)D concentration as a reflection of the total vitamin D intake. Furthermore, the limited number of subjects with low 25(OH)D concentration may have restrained our analyses. We used multiple outcome variables, as we wanted to evaluate growth across the infantile period. The multiple outcome variables increase the possibility that some associations arise by chance. However, results are parallel with each other. The strength of our study is the varied and in-depth approach to analyze the relationships among Pregnancy, UCB, and Infant 25(OH)D on infant growth. In addition, we were able to adjust our analyses for several potential confounders to identify the independent role of vitamin D in growth regulation.

## Conclusion

In our large cohort, high 25(OH)D concentrations in pregnancy, UCB, and infancy were associated with slower growth in infants at 6 and 12 months of age. Overall, our findings suggest an inverse U-shaped association between vitamin D status and infant postnatal growth. Although the underlying mechanisms and direct clinical implications remain to be further explored, our results indicate that, in Finland, an adequate maternal and infant vitamin D status has been achieved with a daily vitamin D supplementation of 10 μg and with vitamin D food fortification. We urge caution in aiming for a higher maternal or infant 25(OH)D concentration with excessive supplementation, as this might have unexpected and possibly disadvantageous effects on infant growth.

## Acknowledgments

We thank the research nurses Sirpa Nolvi, Rhea Paajanen, Nea Boman, and Päivi Turunen for assistance in data collection, laboratory technician Sari Lindén for the work on this study, the midwives and laboratory technicians at Kätilöopisto Maternity Hospital for obtaining UCB samples, and biostatistician Paula Bergman (University of Helsinki and Helsinki University Hospital) for advice during data analysis. Most importantly, we also thank all of the families who participated in this study.

***Financial Support:*** This work was supported by the Academy of Finland, Governmental Subsidy for Clinical Research, Foundation for Pediatric Research, Finska Läkaresällskapet, Folkhälsan Research Foundation, Sigrid Jusélius Foundation, Swedish Childhood Cancer Foundation, Stiftelsen Dorothea Olivia, Karl Walter and Jarl Walter Perkléns Minne, Päivikki and Sakari Sohlberg Foundation, Juho Vainio Foundation, Orion Research Foundation, Instrumentarium Science Foundation, the Paulo Foundation, the Finnish Medical Foundation, Victoriastiftelsen, European Commission, the Novo Nordisk Foundation, the Signe and Ane Gyllenberg Foundation, and the Yrjö Jahnsson Foundation.

***Clinical Trial Information:*** ClinicalTrials.gov no. NCT01723852 (registered 8 November 2012).

***Author Contributions:*** H.H.H.-a. analyzed the data and wrote the first draft of the manuscript. H.H.H.-a., E.K., and O.M. planned the work. H.H.H.-a., E.M.H.-S., J.R., S.M.V., M.E.-C., O.M.H., T.K.H., and H.V. participated in acquisition of the data. H.H.H.-a., E.K., E.M.H.-S., J.R., S.M.V., M.E.-C., O.M.H., T.K.H., H.V., S.A., and O.M. participated in interpretation of the results, writing the manuscript, and approving the final version. E.M.H.-S., O.M.H., H.V., S.A., and O.M. initialized the study.

***Correspondence and Reprint Requests:*** Outi Mäkitie, PhD, Folkhälsan Institute of Genetics, PO Box 63, University of Helsinki, Helsinki FIN-00014, Finland. E-mail: outi.makitie@helsinki.fi; or Helena H. Hauta-alus, MSc, Children's Hospital, University of Helsinki and Helsinki University Hospital, Biomedicum 2C, PO Box 705, Helsinki FI-00020, Finland. E-mail helena.hauta-alus@helsinki.fi.

***Disclosure Summary:*** The authors have nothing to disclose.

## References

1. Weinert LS, Silveiro SP. Maternal-fetal impact of vitamin D deficiency: a critical review. *Matern Child Health J*. 2015;**19**(1):94–101.
2. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. *BMJ*. 2013;**346**:f1169.
3. Roth DE, Leung M, Mesfin E, Qamar H, Watterworth J, Papp E. Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. *BMJ*. 2017;**359**:j5237.
4. Viljakainen HT, Korhonen T, Hytinantti T, Laitinen EK, Andersson S, Mäkitie O, Lamberg-Allardt C. Maternal vitamin D status affects bone growth in early childhood--a prospective cohort study. *Osteoporos Int*. 2011;**22**(3):883–891.
5. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, Godfrey KM, Cooper C; Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr*. 2008;**62**(1):68–77.
6. Gould JF, Anderson AJ, Yelland LN, Smithers LG, Skeaff CM, Zhou SJ, Gibson RA, Makrides M. Association of cord blood vitamin D with early childhood growth and neurodevelopment. *J Paediatr Child Health*. 2017;**53**(1):75–83.
7. van Eijsden M, Snijder MB, Brouwer I, Vrijkotte TG. Maternal early-pregnancy vitamin D status in relation to linear growth at the age of 5-6 years: results of the ABCD cohort. *Eur J Clin Nutr*. 2013;**67**(9):972–977.
8. Ong YL, Quah PL, Tint MT, Aris IM, Chen LW, van Dam RM, Heppe D, Saw SM, Godfrey KM, Gluckman PD, Chong YS, Yap F, Lee YS, Foong-Fong Chong M. The association of maternal vitamin D status with infant birth outcomes, postnatal growth and adiposity in the first 2 years of life in a multi-ethnic Asian population: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort study. *Br J Nutr*. 2016;**116**(4):621–631.
9. Roth DE, Perumal N, Al Mahmud A, Baqui AH. Maternal vitamin D3 supplementation during the third trimester of pregnancy: effects on infant growth in a longitudinal follow-up study in Bangladesh. *J Pediatr*. 2013;**163**(6):1605–1611.e3.
10. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Mäkitie O, Ramos-Abad L, Ward L, DiMeglio LA, Atapattu N, Cassinelli H, Braegger C, Pettifor JM, Seth A, Idris HW, Bhatia V, Fu J, Goldberg G, Sävendahl L, Khadgawat R, Pludowski P, Maddock J, Hyppönen E, Oduwole A, Frew E, Aguiar M, Tulchinsky T, Butler G, Högler W. Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab*. 2016;**101**(2):394–415.
11. Trilok-Kumar G, Kaur M, Rehman AM, Arora H, Rajput MM, Chugh R, Kurpad A, Sachdev HS, Filteau S. Effects of vitamin D supplementation in infancy on growth, bone parameters, body composition and gross motor development at age 3-6 years: follow-up of a randomized controlled trial. *Int J Epidemiol*. 2015;**44**(3):894–905.
12. Gallo S, Comeau K, Vanstone C, Agellon S, Sharma A, Jones G, L'Abbé M, Khamessan A, Rodd C, Weiler H. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. *JAMA*. 2013;**309**(17):1785–1792.
13. Raulio S, Erlund I, Männistö S, Sarlio-Lähteenkorva S, Sundvall J, Tapanainen H, Vartiainen E, Virtanen S. Successful nutrition policy: Improvement of vitamin D intake and status in Finnish adults over the last decade. *Eur J Public Health*. 2017;**27**(2):268–273.
14. Hauta-alus HH, Korkalo L, Holmlund-Suila EM, Rosendahl J, Valkama SM, Enlund-Cerullo M, Helve OM, Hytinantti TK, Mäkitie OM, Andersson S, Viljakainen HT. Food and nutrient intake and nutrient sources in 1-year-old infants in Finland: A cross-sectional analysis. *Nutrients*. 2017;**9**(12):E1309.
15. Helve O, Viljakainen H, Holmlund-Suila E, Rosendahl J, Hauta-alus H, Enlund-Cerullo M, Valkama S, Heinonen K, Räikkonen K, Hytinantti T, Mäkitie O, Andersson S. Towards evidence-based vitamin D supplementation in infants: Vitamin D intervention in infants (VIDI) - study design and methods of a randomised controlled double-blinded intervention study. *BMC Pediatr*. 2017;**17**(1):91.
16. Hauta-alus HH, Holmlund-Suila EM, Rita HJ, Enlund-Cerullo M, Rosendahl J, Valkama SM, Helve OM, Hytinantti TK, Surcel HM, Mäkitie OM, Andersson S, Viljakainen HT. Season, dietary factors, and physical activity modify 25-hydroxyvitamin D concentration during pregnancy. *Eur J Nutr*. 2018;**57**(4):1369–1379.
17. Hauta-alus HH, Viljakainen HT, Holmlund-Suila EM, Enlund-Cerullo M, Rosendahl J, Valkama SM, Helve OM, Hytinantti TK, Mäkitie OM, Andersson S. Maternal vitamin D status, gestational diabetes and infant birth size. *BMC Pregnancy Childbirth*. 2017;**17**(1):420.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;**96**(7):1911–1930.
19. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;**96**(1):53–58.

20. Saari A, Sankilampi U, Hannila ML, Kiviniemi V, Kesseli K, Dunkel L. New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. *Ann Med*. 2011;**43**(3):235–248.
21. De Stavola BL, Nitsch D, dos Santos Silva I, McCormack V, Hardy R, Mann V, Cole TJ, Morton S, Leon DA. Statistical issues in life course epidemiology. *Am J Epidemiol*. 2006;**163**(1):84–96.
22. Eckhardt CL, Gernand AD, Roth DE, Bodnar LM. Maternal vitamin D status and infant anthropometry in a US multi-centre cohort study. *Ann Hum Biol*. 2015;**42**(3):215–222.
23. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. *Br J Nutr*. 2010;**104**(1):108–117.
24. Sauder KA, Koeppen HJ, Shapiro ALB, Kalata KE, Stamatoiu AV, Ringham BM, Glueck DH, Norris JM, Dabelea D. Prenatal vitamin D intake, cord blood 25-hydroxyvitamin D, and offspring body composition: The healthy start study. *Nutrients*. 2017;**9**(7):E790.
25. Prentice A, Jarjou LM, Goldberg GR, Bennett J, Cole TJ, Schoenmakers I. Maternal plasma 25-hydroxyvitamin D concentration and birthweight, growth and bone mineral accretion of Gambian infants. *Acta Paediatr*. 2009;**98**(8):1360–1362.
26. Bodnar LM, Catov JM, Zmuda JM, Cooper ME, Parrott MS, Roberts JM, Marazita ML, Simhan HN. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. *J Nutr*. 2010;**140**(5): 999–1006.
27. Zhu P, Tong SL, Hu WB, Hao JH, Tao RX, Huang K, Mou Z, Zhou QF, Jiang XM, Tao FB. Cord blood 25-hydroxyvitamin D and fetal growth in the China-Anhui birth cohort study. *Sci Rep*. 2015;**5**:14930.
28. Arnberg K, Østergård M, Madsen AL, Krarup H, Michaelsen KF, Mølgaard C. Associations between vitamin D status in infants and blood lipids, body mass index and waist circumference. *Acta Paediatr*. 2011;**100**(9):1244–1248.
29. Holmlund-Suila E, Viljakainen H, Hytinantti T, Lamberg-Allardt C, Andersson S, Mäkitie O. High-dose vitamin d intervention in infants--effects on vitamin d status, calcium homeostasis, and bone strength. *J Clin Endocrinol Metab*. 2012;**97**(11):4139–4147.
30. Morley R, Carlin JB, Pasco JA, Wark JD, Ponsonby AL. Maternal 25-hydroxyvitamin D concentration and offspring birth size: effect modification by infant VDR genotype. *Eur J Clin Nutr*. 2009; **63**(6):802–804.
31. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL, Peltonen L, Cooper JD, O'Reilly PF, Houston DK, Glazer NL, Vandenput L, Peacock M, Shi J, Rivadeneira F, McCarthy MI, Anneli P, de Boer IH, Mangino M, Kato B, Smyth DJ, Booth SL, Jacques PF, Burke GL, Goodarzi M, Cheung CL, Wolf M, Rice K, Goltzman D, Hidiroglou N, Ladouceur M, Wareham NJ, Hocking LJ, Hart D, Arden NK, Cooper C, Malik S, Fraser WD, Hartikainen AL, Zhai G, Macdonald HM, Forouhi NG, Loos RJ, Reid DM, Hakim A, Dennison E, Liu Y, Power C, Stevens HE, Jaana L, Vasan RS, Soranzo N, Bojunga J, Psaty BM, Lorentzon M, Foroud T, Harris TB, Hofman A, Jansson JO, Cauley JA, Uitterlinden AG, Gibson Q, Järvelin MR, Karasik D, Siscovick DS, Econs MJ, Kritchevsky SB, Florez JC, Todd JA, Dupuis J, Hyppönen E, Spector TD. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet*. 2010;**376**(9736):180–188.
32. Cadario F, Savastio S, Pozzi E, Capelli A, Dondi E, Gatto M, Zaffaroni M, Bona G. Vitamin D status in cord blood and newborns: Ethnic differences. *Ital J Pediatr*. 2013;**39**:35.
33. Sempos CT, Durazo-Arvizu RA, Dawson-Hughes B, Yetley EA, Looker AC, Schleicher RL, Cao G, Burt V, Kramer H, Bailey RL, Dwyer JT, Zhang X, Gahche J, Coates PM, Picciano MF. Is there a reverse J-shaped association between 25-hydroxyvitamin D and all-cause mortality? Results from the U.S. nationally representative NHANES. *J Clin Endocrinol Metab*. 2013;**98**(7):3001–3009.
34. Rosendahl J, Holmlund-Suila E, Helve O, Viljakainen H, Hauta-alus H, Valkama S, Enlund-Cerullo M, Hytinantti T, Tervahartiala T, Sorsa T, Mäkitie O, Andersson S. 25-hydroxyvitamin D correlates with inflammatory markers in cord blood of healthy newborns. *Pediatr Res*. 2017;**81**(5):731–735.
35. Valkama S, Holmlund-Suila E, Enlund-Cerullo M, Rosendahl J, Hauta-Alus H, Helve O, Hytinantti T, Viljakainen H, Andersson S, Mäkitie O. No severe hypercalcemia with daily vitamin D3 supplementation of up to 30 μg during the first year of life. *Horm Res Paediatr*. 2017;**88**(2):147–154.
36. Goltzman D. Emerging roles for calcium-regulating hormones beyond osteolysis. *Trends Endocrinol Metab*. 2010;**21**(8):512–518.
37. Goltzman D, Hendy GN. The calcium-sensing receptor in bone--mechanistic and therapeutic insights. *Nat Rev Endocrinol*. 2015; **11**(5):298–307.
38. Goltzman D. Functions of vitamin D in bone. *Histochem Cell Biol*. 2018;**149**(4):305–312.
39. Lieben L, Stockmans I, Moermans K, Carmeliet G. Maternal hypervitaminosis D reduces fetal bone mass and mineral acquisition and leads to neonatal lethality. *Bone*. 2013;**57**(1):123–131.
40. Mortensen C, Mølgaard C, Hauger H, Kristensen M, Damsgaard CT. Winter vitamin $D_3$ supplementation does not increase muscle strength, but modulates the IGF-axis in young children [published online ahead of print 15 Feb 2018]. *Eur J Nutr*. doi: 10.1007/s00394-018-1637-x.